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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	**PAPER NUMBER**
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/734,644	BUA, JAY	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-13,15-21 and 23-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-13, 15-21 and 23-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/21/2006 has been entered.

Claims 1-3, 5-13, 15-21 and 23-28 are currently pending and under consideration.

(Note: Claims 13 and 15-21, previously withdrawn, have been rejoined because the claims require the method of claim 1.)

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13, 15-21, 23 and 25-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. THIS IS A NEW MATTER REJECTION.

Claim 13 recites a method of diagnosing breast disease that comprises performing the method of claim 1, then performing a mammography on said patient. While the specification, as originally filed, has support for reducing the mammographic density of breast tissue comprising performing the method of claim 1 than performing a mammography on said patient (page 24, Example 4), the specification, as well as the claims, as originally filed, do not appear to lend support for the limitation of a method of diagnosing breast disease. Applicant is required to cancel the new

matter in the response to this Office Action. Alternatively, applicant is invited to provide sufficient written support for the "limitation" indicated above. See MPEP 714.02 and 2163.06.

Claims 23 and 26 recites the limitation "hydroxymethylcellulose". While the specification and claims, as originally filed, have support for "hydroxypropylcellulose", the specification, as well as the claims, as originally filed, do not appear to lend support for the limitation hydroxymethylcellulose. Applicant is required to cancel the new matter in the response to this Office Action. Alternatively, applicant is invited to provide sufficient written support for the "limitation" indicated above. See MPEP 714.02 and 2163.06.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5-10, 12-13, 15-20, 15-21, 24-25 and 27-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Atkinson et al. (Cancer Epidemiology, Biomarkers & Prevention 1999; 8: 863-866, IDS) as evidenced by Boyd et al. (J. Nat. Cancer Inst. 1995; 87: 670-675, *of record*) and Kolb et al. (Radiology 2002; 225; 165-175, *of record*) in view of Mauvais-Jarvis (US 4,919,937, 1990, IDS) as evidenced by Mauvais-Jarvis (Cancer Research 1986; 46: 1521-1525, *of record*) and in further view of Yamaguchi et al. (US 5,820,877, 1998).

Atkinson et al teach the effects of tamoxifen on mammographic density, wherein mammograms from 94 women who had received tamoxifen for breast cancer and 188 women (without breast cancer) who had not received tamoxifen were visually classified according to the Wolfe pattern (abstract). Specifically, the reference teaches (page 865, Table 2 and page 864, 1st

column, *Data Analysis*) administration of tamoxifen to patients having N1, P1, P2 or DY breast density Wolfe patterns, wherein N1 represents the most lucent pattern and DY represents the most dense pattern. The reference further teaches (page 865, Table 2 and 2nd column, last paragraph) that tamoxifen treatment resulted in a reduction in mammographic breast density. As such, Atkinson et al. conclude (page 866, 1st column, last paragraph) that an additional benefit of reducing breast density by tamoxifen treatment may relate to the effectiveness of mammographic breast screening, wherein the reduction in breast density may provide benefits in terms of diagnosis at an earlier physiological stage and, thus, improved survival rates from breast cancer. Thus, while Atkinson et al. does not explicitly teach that the breast tissues are class III and/or class IV dense breast tissue, a patient having a the most dense DY breast pattern and/ or a P2 pattern on the Wolfe scale would meet the limitation of a Class III or Class IV dense breast composition because as evidenced by Kolb et al., the American College of Radiology has developed a classification system for breast composition, wherein class 3 is breast tissue heterogeneously dense and class 4 is highly dense (page 166, 3rd column, 1st paragraph). Hence, it does not appear that the claimed limitation and/or category result in a manipulative difference between the prior arts disclosure. Moreover, although Atkinson et al. does not explicitly teach that the breast tissues having a DY pattern includes dense tissue that is diffuse or nodular, the claimed limitation would be an inherent property of breast tissue characterized as DY because as evidenced by Boyd et al., DY describes a breast in which the parenchyma is occupied by both diffuse or nodular densities (page 670, 2nd column, 2nd paragraph). Thus, it does not appear that the claimed limitation results in a manipulative difference in the products used when compared to the prior arts disclosure. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int.

Atkinson et al. do not explicitly teach percutaneous administration of 4-hydroxy tamoxifen to a patient having class III or class IV dense breast composition.

Mauvaris-Jarvis et al. teach (column 4, lines 46-53) a method of treating conditions of the breast comprising administering percutaneously an aqueous alcoholic gel comprising trans-4-hydroxy tamoxifen, wherein the aqueous alcoholic gel enables percutaneous penetration to take place and comprises Carbopol ®, ethyl alcohol/water and 0.15g of 4-hydroxy tamoxifen (column 3, lines 29-39). With regards to the conditions of the breast, the patent teaches (column 4, lines 37-39) that the breast conditions include, but are not limited to, benign and cancerous conditions of the breast. Moreover, Mauvaris-Jarvis et al. teach that percutaneous administration of 4-hyrdroxytamoxifen overcomes the harmful side effects associated with oral administration of 10 to 30 mg/day of tamoxifen such as paradoxical stimulation of the ovaries by passing through the cutaneous barrier and being taken up directly by the receptors molecules in the tumors. In addition, Mauvaris-Jarvis et al. teach that 4-hydroxy tamoxifen is a the active form of tamoxifen at the molecular level and has been shown to be twenty to one hundred times more active than tamoxifen as an anti-estrogen at the level of estrogen receptors (column 1, lines 24-32). Thus, while Mauvaris-Jarvis et al. do not specifically teach that the 4-hyroxy tamoxifen is administered as a racemic mixture of both trans and cis isomer, the claimed limitation would be an inherent property of the percutaneous administration of trans-4-hydroxy tamoxifen because as evidenced by Mauvais-Jarvis (Cancer Research 1986; 46: 1521-1525, IDS), percutaneous administration of the trans-4-OHTAM resulted in an equal yield of the cis and trans isomers of 4-OHTAM from breast tissue (page 1522, 2nd column, 6th paragraph). Thus, it does not appear that the claimed limitation results in a manipulative difference in the products used when compared to the prior arts disclosure. Lastly, although Mauvaris-Jarvis et al. teach that the 0.15g of 4-hydroxy is in The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int.

Mauvaris-Jarvis et al. do not explicitly teach that the alcoholic gel comprises 4-hydroxy tamoxifen, ethyl alcohol, isopropyl myristate, hydroxymethylcelluose and a phosphate buffer.

Yamaguchi et al. teach an alcoholic gel formulation suitable for percutaneous administration comprising a phosphate buffer, ethyl alcohol, isopropyl myristate and hydroxypropylcellulose or hyrdroxypropylmethylcellulose (Column 4, lines 38-42 and Column 11, lines 21-26).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to substitute oral tamoxifen administration to a patient suffering from class III as taught Atkinson et al. for percutaneous administration of 4-hydroxy tamoxifen administration in view of the teachings of Mauvaris-Jarvis. One would have been motivated to do so because as taught by Mauvaris-Jarvis, 4-hydroxy tamoxifen is well known in the art to be the active form of tamoxifen at the molecular level, and further, overcomes the harmful side effects associated with oral administration of 10 to 30 mg/day of tamoxifen such as paradoxical stimulation of the ovaries by passing through the cutaneous barrier and being taken up directly by the estrogen receptors. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by substituting oral tamoxifen administration to a patient suffering from class III as taught Atkinson et al. for percutaneous administration of 4-hydroxy tamoxifen administration in view of the teachings of Mauvaris-Jarvis, one would achieve a safe alternative to oral tamoxifen.

Moreover, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the alcoholic gel as taught by Maurvaris-Jarvis to include 4-hydroxy tamoxifen, ethyl alcohol, isopropyl myristate, hydroxymethylcelluose and a phosphate buffer in view of the teachings of Yamaguchi et al.. One would have been motivated to do so because each has been taught in the prior art as being equivalents suitable for the same purpose. As such, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the alcoholic gel as taught by Maurvaris-Jarvis to include 4-hydroxy tamoxifen, ethyl alcohol, isopropyl myristate, hydroxymethylcelluose and a phosphate buffer in view of the teachings of Yamaguchi et al., one would achieve an effective formulation for percutaneous administration.

Lastly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to optimize the amount of 4-hydroxy tamoxifen per amount of gel as taught by Maurvaris-Jarvis. One would have been motivated to do so because the courts have found that differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature

is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Note: In order to expedite prosecution, the Examiner would like to respond to Applicants arguments for the previous rejections as they relate to the instant rejections. In response to the previous rejection, Applicants assert that the primary reference, Mauvais-Jarvis, does not teach or suggest that 4-hydroxy tamoxifen is effective for reducing breast density, as presently claimed and provides no basis for predicting the usefulness of 4-hydrozy tamoxifen in the present methods. Moreover, Applicants assert that the secondary reference, Atkinson, does not even relate to 4-hydroxy tamoxifen or transdermal administration, but allegedly teaches that oral tamoxifen reduces mammographic breast density. In the instant case, Applicants assert that the rejection relies on the premise that because both "tamoxifen and 4-hydroxy tamoxifen have been individually taught in the prior art to be effective at treating conditions of the breast, including... cancer," then "[o]ne of ordinary skill in the art would have a reasonable expectation of success that by administering 4-hydroxy tamoxifen percutaneously... one would achieve [a] method of reducing breast density." However, Applicants assert that tamoxifen and 4-hydroxy tamoxifen have been shown to have varying effects in the same tissue and cells. For example, Applicants assert that tamoxifen but not 4-hydroxy tamoxifen is a potent rat liver carcinogen, see Carthew et al. and Sauvez et al. of record. Additionally, Applicants submit that tamoxifen but not 4-hydroxy tamoxifen initiates apoptosis in p53(-) normal human mammary epithelial cells, see Dietze et al. of record. By contrast, Applicants assert that 4-hydroxy tamoxifen exhibits a significant inhibitory effect on estrone sulphatase activity in mammary cancer cell lines, while tamoxifen has little or no effect in this regard, see Chetrite et al. of record. Thus, the usefulness of 4-hydroxy tamoxifen in methods where tamoxifen has proven useful is not predictable.

These arguments have been carefully considered, but are not found persuasive.

Regarding Applicants arguments pertaining to the individual references, it appears that applicant have argued and discussed the references individually without clearly addressing the combined teachings, particularly in view of the fact that both references represent analogous teachings comprising administration of tamoxifen or a tamoxifen derivative for the treatment of breast disorders. It must be remembered that the references are relied upon in combination and are

not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination. In re Young, 403 F.2d 754, 159 USPQ 725 (CCPA 1968); In re Keller 642 F.2d 413,208 USPQ 871 (CCPA 1981). Furthermore, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the instant case, Maurvaris-Jarvis provides the motivation to substitute 4-hydroxy tamoxifen for tamoxifen in the method taught by Atkinson et al. because Maurvaris-Jarvis teaches that 4-hydroxy tamoxifen is well known in the art to be the active form of tamoxifen at the molecular level, and further, overcomes the harmful side effects associated with oral administration of 10 to 30 mg/day of tamoxifen such as paradoxical stimulation of the ovaries by passing through the cutaneous barrier and being taken up directly by the estrogen receptors. In response to Applicants arguments pertaining to the differences between tamoxifen and 4-hydroxy tamoxifen, the Examiner recognizes that tamoxifen and 4-hydroxy tamoxifen have been shown to have varying effects in the same tissue and cells have been shown to have varying effects in the same tissue and cells. However, the Examiner recognizes that, in addition to both agents being individually taught in the prior art to be effective at treating conditions of the breast such as cancer, 4-hydroxy tamoxifen is well known in the art to be the active form of tamoxifen at the molecular level, and further, overcomes the harmful side effects associated with oral administration of 10 to 30 mg/day of tamoxifen such as paradoxical stimulation of the ovaries by passing through the cutaneous barrier and being taken up directly by the estrogen receptors. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by substituting oral tamoxifen administration to a patient suffering from class III as taught Atkinson et al. for percutaneous administration of 4-hydroxy tamoxifen administration in view of the teachings of Mauvaris-Jarvis, one would achieve a safe alternative to oral tamoxifen.

Therefore, NO claim is allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Patent Examiner
Art Unit 1642

BF